Remarks/Arguments

Claims 44-46 and 49-51 are pending in this application.

I. Claim Rejections Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 44-46 and 49-51 stand rejected under 35 USC 112, first paragraph, for lack of enablement. Specifically, the Examiner asserts that "[t]he specification fails to provide any working examples or sufficient guidance with respect to treating a particular disease." Furthermore, citing Kahan *et al.*, Piccotti *et al.*, and Campo *et al.*, the Examiner concludes that "while the art recognizes the MLR assay as accepted for screening for immunosuppressive molecules in vitro…this biological activity does not correlate to use of the claimed protein in a therapeutically effective manner, as the asserted use of the claimed invention proposes." (Page 3 of the instant Final Office action). For the reasons outlined below, Applicants respectfully disagree.

The specification provides an enabling disclosure for the utility of PRO335 as a stimulator of the proliferation of stimulated T-lymphocytes

Contrary to the Examiner's assertions, Applicants submit that patentable utility for the PRO335 polypeptide is based upon data derived from the mixed leukocyte reaction (MLR) assay. The MLR assay is a well-established and accepted assay in the art for evaluating test compounds for their ability to stimulate T-lymphocyte proliferation *in vitro*. Example 74 of the instant specification shows that PRO335 tested positive in the mixed lymphocyte reaction (MLR) assay, demonstrating that PRO335 is active as a stimulator of the proliferation of stimulated T-lymphocytes, and therefore has utility, at the very least, as a research tool for activating T cells in vitro. For example, the instant specification discloses that "[t]he membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction." (page 2 of the instant specification) In addition, PRO335 may also have utility in the treatment of conditions where the enhancement of an immune response would be beneficial. However, Applicants reiterate that they are not required to provide clinical data to support such a utility. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to be marketed in the United States. Scott v. Finney, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994). Indeed, in Nelson v. Bowler, 626 F.2d 853, 856, 206 U.S.P.Q.

881, 883 (C.C.P.A. 1980), the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. Induction of T cell proliferation is an example of such a pharmacological activity measured by the MLR assay. As the assay itself is well established in the art and adequately disclosed in the instant specification, the enablement requirement is also satisfied.

Applicants note that not only has the Examiner acknowledged that the MLR assay is an art accepted assay for identifying immunomodulatory compounds (see pages 3 and 11, paragraph 1 of the Final Office Action mailed February 1, 2007 and page 2 of the Office Action mailed April 8, 2008), but also the utility and enablement of related molecules based on the disclosed MLR assay have been recognized and allowed by the USPTO. (see e.g. US 7,557,192 (directed to anti-PRO335 antibodies)) Thus, given the knowledge in the art together with the disclosure in the instant specification, the skilled artisan would know how to use PRO335 as a T cell stimulator of proliferation.

The mixed lymphocyte reaction (MLR) assay is an art accepted assay for identifying immunomodulatory compounds

The Examiner cites Kahan *et al.*, Piccotti *et al.*, and Campo *et al.*, and concludes that "while the art recognizes the MLR assay as accepted for screening for immunosuppressive molecules in vitro…this biological activity does not correlate to use of the claimed protein in a therapeutically effective manner, as the asserted use of the claimed invention proposes." (Pages 3-6 of the instant Final Office Action).

Applicants reiterate that the instant claims are directed to PRO335 polypeptides where the polypeptides have a specific and useful function (*i.e.* as "immunostimulants" useful for stimulating the proliferation of T-lymphocytes and perhaps boosting the immune system of an animal. Applicants submit that, the instant specification, at least in Example 74, page 208, line 27, and the disclosure of the Fong declaration (submitted with Applicants' response of October 25, 2004), describe the mixed lymphocyte reaction (MLR) assay, which the Examiner has acknowledged as sufficient to establish patentable utility under 35 U.S.C. §101 for the nucleic acids encoding the PRO335 polypeptide. The positive result for PRO335 in the MLR assay demonstrates that PRO335 is active as a stimulator of the proliferation of stimulated T-lymphocytes. Accordingly, Applicants submit that when the proper legal standard is applied,

one should reach the conclusion that the present specification provides ample guidance to allow the skilled artisan to make and use PRO335 polypeptides that are useful for stimulating T-cell proliferation and perhaps in the treatment of conditions requiring immunostimulation, and further, one skilled in the art would know how to use these polypeptides without any undue experimentation.

With regard to the Examiner's citation of Kahan *et al.*, Picotti *et al.* and Campo *et al.*, Applicants submit, as previously presented, that the Examiner has not correctly characterized the teachings of these references. By contrast, these references in combination with those cited by Applicants, demonstrate that the art as a whole recognizes that the mixed lymphocyte reaction (MLR) is a widely used *in vitro* assay for identifying immunomodulatory compounds. Thus, while there are instances of unpredictability in some studies using the MLR assay, there are many more studies showing the usefulness and predictable results using MLR, as exemplified by the studies by Picotti, Landolfo and the IFN-gamma study and all the references submitted by the Applicants in this response. Therefore, the teachings within Kahan *et al.*, Piccotti *et al.*, Campo *et al.*, in fact, support the usefulness of the MLR assay.

Thus, the art as a whole, at the time of filing of the application, clearly establishes that the mixed lymphocyte reaction (MLR) is a widely used *in vitro* assay for identifying immunomostimulatory compounds and that the positive result as a stimulator in the MLR assay is widely accepted as a valid indication of T cell activation, which may be utilized for research or therapeutic purposes. Applicants note that Dr. Fong's conclusions are consistent with what is accepted in the art. Accordingly, one skilled in the art would know how to use the compounds for the asserted purpose. Therefore, based on the art's teachings about the immunostimulatory activity of molecules, as a result of a positive MLR assay, would provide sufficient correlation to one skilled in the art, such that they would use the identified compounds in the stimulation of the immune system.

In summary, the lack of enablement rejection of the claims under 35 U.S.C. 112, first paragraph, made in the present Final Office Action assumes that the claimed invention is to be used for therapeutic enhancement of the immune response and alleges that the results of Example 74 (MLR assay) in the specification are not sufficient to support the enablement of the claims since there is no indication that PRO335 could be used to any therapeutic effect for the treatment of diseases such as cancer or HIV. However, Applicants once again point out that the instant

invention is directed to a product, not a method of treatment, and the product does not require a specifically designated use such as for treating a disease, therefore, it would not be required that the claimed polypeptide has to be enabled for therapeutic uses in order to meet the requirement of 35 U.S.C. 112, first paragraph, and it can be enabled for other uses. For example, the polypeptide can be used for a purpose such as for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. The technology of assessing T-cell activation through proliferation in the MLR assay has been well established in the art. Thus, based on the examples and specific teachings provided in the specification and general knowledge in the art, one skilled in the art at the priority date of the present application would have clearly known how to use the invention within the full scope of the claims pending. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

CONCLUSION

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any additional fees for extension of time, or credit overpayment to Deposit Account No. 50-2387 (Attorney Docket No.: **24126-191 (GNE-1618P2C46)**. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: September 22, 2010

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